

NPLATE- romiplostim injection, powder, lyophilized, for solution

Amgen Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NPLATE safely and effectively. See full prescribing information for NPLATE.

NPLATE® (romiplostim) for injection, for subcutaneous use
Initial U.S. Approval: 2008

----- **INDICATIONS AND USAGE** -----

Nplate is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Limitations of Use:

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP.
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- Nplate should not be used in an attempt to normalize platelet counts. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Initial dose of 1 mcg/kg once weekly as a subcutaneous injection. (2.1)
- Adjust weekly dose by increments of 1 mcg/kg to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding. (2.1)
- Do not exceed the maximum weekly dose of 10 mcg/kg. Do not dose if platelet count is $> 400 \times 10^9/L$. (2.1)
- Discontinue Nplate if platelet count does not increase after 4 weeks at the maximum dose. (2.1)
- Do not shake during reconstitution; protect reconstituted Nplate from light; administer reconstituted Nplate within 24 hours. (2.2)
- The injection volume may be very small. Use a syringe with graduations to 0.01 mL. (2.2)
- Discard any unused portion of the single-dose vial. (2.2)

----- **DOSAGE FORMS AND STRENGTHS** -----

- For injection: 250 mcg or 500 mcg of deliverable romiplostim as a lyophilized powder in single-dose vials. (3)

----- **CONTRAINDICATIONS** -----

None (4)

----- **WARNINGS AND PRECAUTIONS** -----

- In some patients with MDS, Nplate increases blast cell counts and increases the risk of progression to acute myelogenous leukemia. (5.1)
- Thrombotic/thromboembolic complications may result from increases in platelet counts with Nplate use. Portal vein thrombosis has been reported in patients with chronic liver disease receiving Nplate. (5.2)
- If severe thrombocytopenia develops during Nplate treatment, assess patients for the formation of neutralizing antibodies. (5.3)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions ($\geq 5\%$ higher patient incidence in Nplate versus placebo) are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia. Headache was the most commonly reported adverse reaction that did not occur at $\geq 5\%$ higher patient incidence in Nplate versus placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **USE IN SPECIFIC POPULATIONS** -----

- **Pregnancy:** Based on animal data, Nplate may cause fetal harm. (8.1)
- **Nursing Mothers:** A decision should be made to discontinue Nplate or nursing, taking into account the importance of Nplate to the mother. (8.3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Recommended Dosage Regimen
 - 2.2 Preparation and Administration
 - 2.3 Use of Nplate With Concomitant Medical ITP Therapies
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Risk of Progression of Myelodysplastic Syndromes to Acute Myelogenous Leukemia
 - 5.2 Thrombotic/Thromboembolic Complications
 - 5.3 Loss of Response to Nplate
 - 5.4 Laboratory Monitoring
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Postmarketing Experience
 - 6.3 Immunogenicity
- 7 DRUG INTERACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Renal Impairment
 - 8.7 Hepatic Impairment
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES**
 - 14.1 Chronic ITP
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Nplate is indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Limitations of Use:

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP [see *Warnings and Precautions (5.1)*].
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding [see *Warnings and Precautions (5.2)*].
- Nplate should not be used in an attempt to normalize platelet counts [see *Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Regimen

Use the lowest dose of Nplate to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding. Administer Nplate as a weekly subcutaneous injection with dose adjustments based upon the platelet count response.

The prescribed Nplate dose may consist of a very small volume (eg, 0.15 mL). Administer Nplate only with a syringe that contains 0.01 mL graduations.

Initial Dose

The initial dose for Nplate is 1 mcg/kg based on actual body weight.

Dose Adjustments

Use the actual body weight at initiation of therapy, then adjust the weekly dose of Nplate by increments of 1 mcg/kg until the patient achieves a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg. In clinical studies, most patients who responded to Nplate achieved and maintained platelet counts $\geq 50 \times 10^9/L$ with a median dose of 2 mcg/kg.

During Nplate therapy, assess CBCs, including platelet counts, weekly until a stable platelet count ($\geq 50 \times 10^9/L$ for at least 4 weeks without dose adjustment) has been achieved. Obtain CBCs, including platelet counts, monthly thereafter.

Adjust the dose as follows:

- If the platelet count is $< 50 \times 10^9/L$, increase the dose by 1 mcg/kg.
- If platelet count is $> 200 \times 10^9/L$ for 2 consecutive weeks, reduce the dose by 1 mcg/kg.
- If platelet count is $> 400 \times 10^9/L$, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to $< 200 \times 10^9/L$, resume Nplate at a dose reduced by 1 mcg/kg.

Discontinuation

Discontinue Nplate if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of Nplate therapy at the maximum weekly dose of 10 mcg/kg [see *Warnings and Precautions (5.3)*]. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Nplate [see *Warnings and Precautions (5.4)*].

2.2 Preparation and Administration

To mitigate against medication errors (both overdose and underdose), ensure that these preparation and administration instructions are followed.

Calculate the dose and reconstitute with the correct volume of sterile water for injection. Withdraw the

appropriate volume of the calculated dose from the vial. Only administer subcutaneously [see *Overdosage (10)*].

Nplate is supplied in single-dose vials as a sterile, preservative-free, white lyophilized powder that must be reconstituted as outlined in Table 1 and administered using a syringe with 0.01 mL graduations. Using aseptic technique, reconstitute Nplate with preservative-free Sterile Water for Injection, USP, as described in Table 1. Do not use bacteriostatic water for injection.

Table 1. Reconstitution of Nplate Single-Dose Vials

Nplate Single-Dose Vial	Total Vial Content of Nplate*		Sterile Water for Injection**		Deliverable Product and Volume	Final Concentration
250 mcg	375 mcg	add	0.72 mL	=	250 mcg in 0.5 mL	500 mcg/mL
500 mcg	625 mcg	add	1.2 mL	=	500 mcg in 1 mL	500 mcg/mL

* Total vial content includes overfill to ensure delivery of 250 mcg or 500 mcg.

** Use preservative-free Sterile Water for Injection.

Gently swirl and invert the vial to reconstitute. Avoid excess or vigorous agitation: **DO NOT SHAKE**. Generally, dissolution of Nplate takes less than 2 minutes. The reconstituted Nplate solution should be clear and colorless. Visually inspect the reconstituted solution for particulate matter and/or discoloration. Do not administer Nplate if particulate matter and/or discoloration is observed.

Reconstituted Nplate can be kept at room temperature (25°C/77°F) or refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours prior to administration. Protect the reconstituted product from light.

To determine the injection volume to be administered, first identify the patient's total dose in micrograms (mcg) using the dosing information in Section 2.1. For example, a 75 kg patient initiating therapy at 1 mcg/kg will begin with a dose of 75 mcg. Next, calculate the volume of Nplate solution that is given to the patient by dividing the microgram dose by the concentration of the reconstituted Nplate solution (500 mcg/mL). For this patient example, the 75 mcg dose is divided by 500 mcg/mL, resulting in an injection volume of 0.15 mL.

As the injection volume may be very small, use a syringe with graduations to 0.01 mL. Verify that the syringe contains the correct dosage.

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than one dose from a vial.

2.3 Use of Nplate With Concomitant Medical ITP Therapies

Nplate may be used with other medical ITP therapies, such as corticosteroids, danazol, azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. If the patient's platelet count is $\geq 50 \times 10^9/L$, medical ITP therapies may be reduced or discontinued [see *Clinical Studies (14.1)*].

3 DOSAGE FORMS AND STRENGTHS

For injection: 250 mcg or 500 mcg of deliverable romiplostim as a sterile, lyophilized, solid white powder in single-dose vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Progression of Myelodysplastic Syndromes to Acute Myelogenous Leukemia

Progression from myelodysplastic syndromes (MDS) to acute myelogenous leukemia (AML) has been observed in clinical trials with Nplate.

A randomized, double-blind, placebo-controlled trial enrolling patients with severe thrombocytopenia and International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS was terminated due to more cases of AML observed in the Nplate arm. This trial consisted of a 58-week study period with a 5-year long-term follow-up phase. The subjects were randomized 2:1 to treatment with Nplate or placebo (167 Nplate, 83 placebo). During the 58-week study period, progression to AML occurred in 10 (6.0%) subjects in the Nplate arm and 4 (4.8%) subjects in the placebo arm (hazard ratio [95%CI] = 1.20 [0.38, 3.84]). Of the 250 subjects, 210 (84.0%) entered the long-term follow-up phase of this study. With 5-years of follow-up, 29 (11.6%) subjects showed progression to AML, including 20/168 (11.9%) subjects in the Nplate arm versus 9/82 (11.0%) subjects in the placebo arm (HR [95% CI] = 1.06 [0.48, 2.33]). The incidence of death (overall survival) was 55.7% (93/167) in the Nplate arm versus 54.2% (45/83) in the placebo arm (HR [95% CI] = 1.03 [0.72, 1.47]). In the baseline low IPSS group, there was a higher incidence of death in the Nplate arm [41.3% (19/46)] compared to the placebo arm [30.4% (7/23)] [HR (95% CI) = 1.59 (0.67, 3.80)].

In a single-arm trial of Nplate given to 72 subjects with thrombocytopenia-related MDS, 8 (11.1%) subjects were reported as having possible disease progression, of which 3 (4.2%) had confirmation of AML during follow-up. In addition, in 3 (4.2%) subjects, increased peripheral blood blast cell counts decreased to baseline after discontinuation of Nplate.

Nplate is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

5.2 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with Nplate use. Portal vein thrombosis has been reported in patients with chronic liver disease receiving Nplate.

To minimize the risk for thrombotic/thromboembolic complications, do not use Nplate in an attempt to normalize platelet counts. Follow the dose adjustment guidelines [see *Dosage and Administration (2.1)*].

5.3 Loss of Response to Nplate

Hyporesponsiveness or failure to maintain a platelet response with Nplate should prompt a search for causative factors, including neutralizing antibodies to Nplate [see *Adverse Reactions (6.3)*]. To detect antibody formation, submit blood samples to Amgen (1-800-772-6436). Amgen will assay these samples for antibodies to Nplate and thrombopoietin (TPO). Discontinue Nplate if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the highest weekly dose of 10 mcg/kg.

5.4 Laboratory Monitoring

Obtain CBCs, including platelet counts, weekly during the dose adjustment phase of Nplate therapy and then monthly following establishment of a stable Nplate dose. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Nplate [see *Dosage and Administration (2.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections:

- Progression of Myelodysplastic Syndromes [see *Warnings and Precautions (5.1)*]
- Thrombotic/Thromboembolic Complications [see *Warnings and Precautions (5.2)*]
- Loss of Response to Nplate [see *Warnings and Precautions (5.3)*]
- Laboratory Monitoring [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect Nplate exposure to 271 patients with chronic ITP, aged 18 to 88, of whom 62% were female. Nplate was studied in two randomized, placebo-controlled, double-blind studies that were identical in design, with the exception that Study 1 evaluated nonsplenectomized patients with ITP and Study 2 evaluated splenectomized patients with ITP. Data are also reported from an open-label, single-arm study in which patients received Nplate over an extended period of time. Overall, Nplate was administered to 114 patients for at least 52 weeks and 53 patients for at least 96 weeks.

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving Nplate and 32% of patients receiving placebo. Headaches were usually of mild or moderate severity. Table 2 presents adverse drug reactions from Studies 1 and 2 with a $\geq 5\%$ higher patient incidence in Nplate versus placebo. The majority of these adverse drug reactions were mild to moderate in severity.

Table 2. Adverse Drug Reactions Identified in Two Placebo-Controlled Studies

Preferred Term	Nplate (n = 84)	Placebo (n = 41)
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in Extremity	13%	5%
Abdominal Pain	11%	0%
Shoulder Pain	8%	0%
Dyspepsia	7%	0%
Paresthesia	6%	0%

Among 142 patients with chronic ITP who received Nplate in the single-arm extension study, the incidence rates of the adverse reactions occurred in a pattern similar to those reported in the placebo-controlled clinical studies.

Bone Marrow Reticulin Formation and Collagen Fibrosis

Nplate administration may increase the risk for development or progression of reticulin fiber formation within the bone marrow. This formation may improve upon discontinuation of Nplate. In a clinical trial, one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate therapy.

An open-label clinical trial prospectively evaluated changes in bone marrow reticulin formation and collagen fibrosis in adult patients with ITP treated with Nplate or a non-US approved romiplostim product. Patients were administered romiplostim by SC injection once weekly for up to 3 years. Based on cohort assignment at time of study enrollment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1), year 2 (cohort 2), or year 3 (cohort 3) in comparison to the baseline bone marrow at start of the trial. Patients were evaluated for bone marrow reticulin formation and collagen fibrosis using the modified Bauermeister grading scale. From the total of 169 patients enrolled in the 3 cohorts, 132 (78%) patients were evaluable for bone marrow collagen fibrosis and 131 (78%) patients

were evaluable for bone marrow reticulin formation. Two percent (2/132) of patients (both from cohort 3) developed Grade 4 findings (presence of collagen). There was no detectable bone marrow collagen in one patient on repeat testing 12 weeks after discontinuation of romiplostim. Progression of bone marrow reticulin formation (increase greater than or equal to 2 grades or more) or an increase to Grade 4 (presence of collagen) was reported in 7% (9/131) of patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Nplate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Erythromelalgia
- Hypersensitivity
- Angioedema

6.3 Immunogenicity

As with all therapeutic proteins, patients may develop antibodies to the therapeutic protein. Patients were screened for immunogenicity to romiplostim using a BIAcore-based biosensor immunoassay.

This assay is capable of detecting both high- and low-affinity binding antibodies that bind to romiplostim and cross-react with TPO. The samples from patients that tested positive for binding antibodies were further evaluated for neutralizing capacity using a cell-based bioassay.

In clinical studies in patients with ITP, the incidence of preexisting antibodies to romiplostim was 5% (53/1112) and the incidence of binding antibody development during treatment with Nplate or a non-US approved romiplostim product was 4% (50/1112). The incidence of preexisting antibodies to endogenous TPO was 4% (40/1112) and the incidence of binding antibody development to endogenous TPO during treatment was 3% (38/1112). Of the patients with positive binding antibodies that developed to romiplostim or to TPO, five patients had neutralizing activity to romiplostim and none had neutralizing activity to TPO. No apparent correlation was observed between antibody activity and clinical effectiveness or safety.

A postmarketing registry study involving patients with thrombocytopenia on Nplate or a non-US approved romiplostim product was conducted to assess the long-term consequences of the anti-romiplostim antibodies. Patients who lacked response or lost response to Nplate or a non-US approved romiplostim product were enrolled. The incidence of new binding antibody development was 3% (5/186) to romiplostim and 1% (2/186) to TPO. One patient was positive for binding antibodies to both romiplostim and TPO. Of the five patients with positive binding antibodies to romiplostim, two (1%) were positive for neutralizing antibodies to romiplostim only.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to romiplostim with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug interaction studies of Nplate have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Nplate use in pregnant women. In animal

reproduction and developmental toxicity studies, romiplostim crossed the placenta, and adverse fetal effects included thrombocytosis, postimplantation loss, and an increase in pup mortality. Nplate should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In rat and rabbit developmental toxicity studies, no evidence of fetal harm was observed at romiplostim doses up to 11 times (rats) and 82 times (rabbits) the maximum human dose (MHD) based on systemic exposure. In mice at doses 5 times the MHD, reductions in maternal body weight and increased postimplantation loss occurred.

In a prenatal and postnatal development study in rats, at doses 11 times the MHD, there was an increase in perinatal pup mortality. Romiplostim crossed the placental barrier in rats and increased fetal platelet counts at clinically equivalent and higher doses.

Women who become pregnant during Nplate treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

8.3 Nursing Mothers

It is not known whether Nplate is excreted in human milk; however, human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Nplate, a decision should be made whether to discontinue nursing or to discontinue Nplate, taking into account the importance of Nplate to the mother and the known benefits of nursing.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients (< 18 years) have not been established.

8.5 Geriatric Use

Of the 271 patients who received Nplate in ITP clinical studies, 55 (20%) were age 65 and over, and 27 (10%) were 75 and over. No overall differences in safety or efficacy have been observed between older and younger patients in the placebo-controlled studies, but greater sensitivity of some older individuals cannot be ruled out. In general, dose adjustment for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

No clinical studies were conducted in patients with renal impairment.

8.7 Hepatic Impairment

No clinical studies were conducted in patients with hepatic impairment.

10 OVERDOSAGE

Overdoses due to medication errors have been reported in patients receiving Nplate. In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In this case, discontinue Nplate and monitor platelet counts. Reinitiate treatment with Nplate in accordance with dosing and administration recommendations [see *Dosage and Administration* (2.1, 2.2)].

11 DESCRIPTION

Romiplostim, a member of the TPO mimetic class, is an Fc-peptide fusion protein (peptibody) that activates intracellular transcriptional pathways leading to increased platelet production via the TPO receptor (also known as cMpl). The peptibody molecule contains two identical single-chain subunits, each consisting of human immunoglobulin IgG1 Fc domain, covalently linked at the C-terminus to a peptide containing two thrombopoietin receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO. Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E coli*).

Nplate is supplied as a sterile, preservative-free, lyophilized, solid white powder for subcutaneous injection. Two vial presentations are available, which contain a sufficient amount of active ingredient to provide either 250 mcg or 500 mcg of deliverable romiplostim, respectively. Each single-dose 250 mcg vial of Nplate contains the following: 375 mcg romiplostim, 30 mg mannitol, 15 mg sucrose, 1.2 mg L-histidine, 0.03 mg polysorbate 20, and sufficient HCl to adjust the pH to a target of 5.0. Each single-dose 500 mcg vial of Nplate contains the following: 625 mcg romiplostim, 50 mg mannitol, 25 mg sucrose, 1.9 mg L-histidine, 0.05 mg polysorbate 20, and sufficient HCl to adjust the pH to a target of 5.0 [see *Dosage and Administration* (2.2)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nplate increases platelet production through binding and activation of the TPO receptor, a mechanism analogous to endogenous TPO.

12.2 Pharmacodynamics

In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet counts. After a single subcutaneous dose of 1 to 10 mcg/kg Nplate in patients with chronic ITP, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2- to 3-week period. The platelet counts were above $50 \times 10^9/L$ for seven out of eight patients with chronic ITP who received six weekly doses of Nplate at 1 mcg/kg.

12.3 Pharmacokinetics

In the long-term extension study in patients with ITP receiving weekly treatment of Nplate subcutaneously, the pharmacokinetics of romiplostim over the dose range of 3 to 15 mcg/kg indicated that peak serum concentrations of romiplostim were observed about 7 to 50 hours post dose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum concentrations was observed (n = 4) after six weekly doses of Nplate (3 mcg/kg). The accumulation at higher doses of romiplostim is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of romiplostim has not been evaluated. The mutagenic potential of romiplostim has not been evaluated. Romiplostim had no effect on the fertility of rats at doses up to 37 times the MHD based on systemic exposure.

13.2 Animal Toxicology and/or Pharmacology

In a 4-week repeat-dose toxicity study in which rats were dosed subcutaneously three times per week, romiplostim caused extramedullary hematopoiesis, bone hyperostosis, and marrow fibrosis at clinically

equivalent and higher doses. In this study, these findings were not observed in animals after a 4-week post treatment recovery period. Studies of long-term treatment with romiplostim in rats have not been conducted; therefore, it is not known if the fibrosis of the bone marrow is reversible in rats after long-term treatment.

14 CLINICAL STUDIES

14.1 Chronic ITP

The safety and efficacy of Nplate were assessed in two double-blind, placebo-controlled clinical studies and in an open-label extension study.

Studies 1 and 2

In Studies 1 and 2, patients with chronic ITP who had completed at least one prior treatment and had a platelet count of $\leq 30 \times 10^9/L$ prior to study entry were randomized (2:1) to 24 weeks of Nplate (1 mcg/kg subcutaneous [SC]) or placebo. Prior ITP treatments in both study groups included corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (ie, corticosteroids, IVIG, platelet transfusions, and anti-D immunoglobulin) were permitted for bleeding, wet purpura, or if the patient was at immediate risk for hemorrhage. Patients received single weekly SC injections of Nplate, with individual dose adjustments to maintain platelet counts ($50 \times 10^9/L$ to $200 \times 10^9/L$).

Study 1 evaluated patients who had not undergone a splenectomy. The patients had been diagnosed with ITP for approximately 2 years and had received a median of three prior ITP treatments. Overall, the median platelet count was $19 \times 10^9/L$ at study entry. During the study, the median weekly Nplate dose was 2 mcg/kg (25th–75th percentile: 1–3 mcg/kg).

Study 2 evaluated patients who had undergone a splenectomy. The patients had been diagnosed with ITP for approximately 8 years and had received a median of six prior ITP treatments. Overall, the median platelet count was $14 \times 10^9/L$ at study entry. During the study, the median weekly Nplate dose was 3 mcg/kg (25th–75th percentile: 2–7 mcg/kg).

Study 1 and 2 outcomes are shown in Table 3. A durable platelet response was the achievement of a weekly platelet count $\geq 50 \times 10^9/L$ for any 6 of the last 8 weeks of the 24-week treatment period in the absence of rescue medication at any time. A transient platelet response was the achievement of any weekly platelet counts $\geq 50 \times 10^9/L$ for any 4 weeks during the treatment period without a durable platelet response. An overall platelet response was the achievement of either a durable or a transient platelet response. Platelet responses were excluded for 8 weeks after receiving rescue medications.

Table 3. Results From Placebo-Controlled Studies^a

Outcomes	Study 1 Nonsplenectomized Patients		Study 2 Splenectomized Patients	
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)
Platelet Responses and Rescue Therapy				
Durable Platelet Response, n (%)	25 (61%)	1 (5%)	16 (38%)	0 (0%)
Overall Platelet Response, n (%)	36 (88%)	3 (14%)	33 (79%)	0 (0%)
Number of Weeks With Platelet Counts $\geq 50 \times 10^9/L$, average	15	1	12	0
Requiring Rescue Therapy, n (%)	8 (20%)	13 (62%)	11 (26%)	12 (57%)
Reduction/Discontinuation of Baseline Concurrent ITP Medical Therapy				

Receiving Therapy at Baseline	(n = 11)	(n = 10)	(n = 12)	(n = 6)
Patients Who Had > 25% Dose Reduction in Concurrent Therapy, n (%)	4/11 (36%)	2/10 (20%)	4/12 (33%)	1/6 (17%)
Patients Who Discontinued Baseline Therapy, n (%) ^b	4/11 (36%)	3/10 (30%)	8/12 (67%)	0/6 (0%)

^a All *p* values < 0.05 for platelet response and rescue therapy comparisons between Nplate and placebo.

^b For multiple concomitant baseline therapies, all therapies were discontinued.

In Studies 1 and 2, nine patients reported a serious bleeding event [five (6%) Nplate, four (10%) placebo]. Bleeding events that were Grade 2 severity or higher occurred in 15% of patients treated with Nplate and 34% of patients treated with placebo.

Extension Study

Patients who had participated in either Study 1 or Study 2 were withdrawn from study medications. If platelet counts subsequently decreased to $\leq 50 \times 10^9/L$, the patients were allowed to receive Nplate in an open-label extension study with weekly dosing based on platelet counts. Following Nplate discontinuation in Studies 1 and 2, seven patients maintained platelet counts of $\geq 50 \times 10^9/L$. Among 100 patients who subsequently entered the extension study, platelet counts were increased and sustained regardless of whether they had received Nplate or placebo in the prior placebo-controlled studies.

The majority of patients reached a median platelet count of $50 \times 10^9/L$ after receiving one to three doses of Nplate, and these platelet counts were maintained throughout the remainder of the study with a median duration of Nplate treatment of 60 weeks and a maximum duration of 96 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

Nplate is supplied in single-dose vials that deliver 250 mcg (NDC 55513-221-01) and 500 mcg (NDC 55513-222-01) of romiplostim.

Store Nplate vials in their carton to protect from light until time of use. Keep Nplate vials refrigerated at 2° to 8°C (36° to 46°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Information for Patients

Prior to treatment, patients should fully understand the risks and benefits of Nplate. Inform patients that the risks associated with long-term administration of Nplate are unknown.

Inform patients of the following risks and considerations for Nplate:

- Nplate therapy is administered to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding; Nplate is not used to normalize platelet counts.
- Following discontinuation of Nplate, thrombocytopenia and risk of bleeding may develop that is worse than that experienced prior to the Nplate therapy.
- Nplate therapy may increase the risk of reticulin fiber formation within the bone marrow. This formation may improve upon discontinuation. Detection of peripheral blood cell abnormalities may necessitate a bone marrow examination.
- Too much Nplate may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications.
- Nplate stimulates certain bone marrow cells to make platelets and increases the risk of progression to acute myelogenous leukemia in patients with myelodysplastic syndromes.

- Platelet counts and CBCs must be performed weekly until a stable Nplate dose has been achieved; thereafter, platelet counts and CBCs must be performed monthly while taking Nplate.
- Patients must be closely monitored with weekly platelet counts and CBCs for at least 2 weeks following Nplate discontinuation.
- Even with Nplate therapy, patients should continue to avoid situations or medications that may increase the risk for bleeding.

Nplate[®] (romiplostim)

Manufactured by:

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

U.S. License No. 1080

Patent: <http://pat.amgen.com/nplate/>

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www.nplate.com

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MEDICATION GUIDE

**Nplate[®] (N-plät)
(romiplostim)
for injection**

What is the most important information I should know about Nplate?

Nplate can cause serious side effects, including:

- **Worsening of a precancerous blood condition to a blood cancer (leukemia).** Nplate is not for use in people with a precancerous condition called myelodysplastic syndromes (MDS) or for any condition other than chronic (lasting a long time) immune thrombocytopenia (ITP). If you have MDS and receive Nplate, your MDS condition may worsen and become an acute leukemia. If MDS worsens to become acute leukemia you may die sooner from the acute leukemia.
- **Higher risk for blood clots.**
 - You may have a higher risk of getting a blood clot if your platelet count becomes high during treatment with Nplate. You may have severe complications or die from some forms of blood clots, such as clots that spread to the lungs or that cause heart attacks or strokes.
 - If you have a chronic liver disease, you may get blood clots in the veins of your liver. This may affect your liver function.

Your healthcare provider will closely monitor your Nplate dose and blood tests, including platelet counts during treatment.

- Injection of too much Nplate may cause a dangerous increase in your blood platelet count and serious side effects.
- Your healthcare provider may change your dose or stop Nplate, depending upon the change in your blood platelet count. You must have blood platelet counts done before you start, during, and after Nplate therapy is stopped.

See “What are the possible side effects of Nplate?” for other side effects of Nplate.

What is Nplate?

Nplate is a man-made protein medicine used to treat low blood platelet counts in adults with chronic immune thrombocytopenia (ITP), when certain other medicines, or surgery to remove your spleen, have not worked well enough.

Nplate is not for use in people with a precancerous condition called myelodysplastic syndrome (MDS) or low platelet count caused by any condition other than chronic (lasting a long time) immune thrombocytopenia (ITP).

Nplate is only used if your low platelet count and medical condition increase your risk of bleeding.

Nplate is used to try to keep your platelet count about 50,000 per microliter in order to lower the risk for bleeding. Nplate is not used to make your platelet count normal.

It is not known if Nplate is safe and effective in children under the age of 18.

Before receiving Nplate, tell your healthcare provider about all your medical conditions, including if you:

- Have had surgery to remove your spleen (splenectomy)
- Have a bone marrow problem, including a blood cancer or MDS
- Have or had a blood clot
- Have chronic liver disease
- Have bleeding problems
- Are pregnant, or plan to become pregnant. It is not known if Nplate will harm your unborn baby.

Pregnancy Surveillance Program: Women who become pregnant during Nplate treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. The purpose of this program is to collect safety information about the health of you and your baby. Contact the program as soon as you become aware of the pregnancy, or ask your healthcare provider to contact the program for you. You or your healthcare provider can get information and enroll in the program by calling 1-800-77-AMGEN (1-800-772-6436).

- Are breastfeeding or plan to breastfeed. It is not known if Nplate passes into your breast milk. You and your healthcare provider should decide if you will take Nplate or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal products. Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive Nplate?

Before you receive Nplate you should first talk with your healthcare provider and understand the benefits and risks of Nplate.

- Nplate is given under the skin (subcutaneous injection) one time each week by your healthcare provider.
- Your healthcare provider will check your platelet count every week and change your dose of Nplate as needed. This will continue until your healthcare provider decides that your dose of Nplate can stay the same. After that, you will need to have blood tests every month. When you stop receiving Nplate, you will need blood tests for at least 2 weeks to check if your platelet count drops too low.
- Tell your healthcare provider about any bruising or bleeding that occurs while you are receiving Nplate.
- If you miss a scheduled dose of Nplate, call your healthcare provider to schedule your next dose as soon as possible.

What should I avoid while receiving Nplate?

Avoid situations that may increase your risk of bleeding, such as missing a scheduled dose of Nplate. You should schedule your next dose as soon as possible and call your healthcare provider.

What are the possible side effects of Nplate?

Nplate may cause serious side effects. See “What is the most important information I should know about Nplate?”

The most common side effects of Nplate are:

-
- | | |
|---------------------------------|--|
| • Headache | • Pain in arms and legs |
| • Joint pain | • Stomach (abdomen) pain |
| • Dizziness | • Shoulder pain |
| • Trouble sleeping | • Indigestion |
| • Muscle tenderness or weakness | • Tingling or numbness in hands and feet |
-

People who take Nplate may have an increased risk of developing new or worsening changes in the bone marrow called “increased reticulatin”. These changes may improve if you stop taking Nplate. Your healthcare provider may need to check your bone marrow for this problem during treatment with Nplate.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Amgen at 1-800-77-AMGEN (1-800-772-6436).

General information about the safe and effective use of Nplate.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Nplate. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Nplate that is written for health professionals.

What are the ingredients in Nplate?

Active ingredient: romiplostim

Inactive ingredients: L-histidine, sucrose, mannitol, polysorbate 20, and hydrochloric acid

Nplate® (romiplostim)

Manufactured by:

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

U.S. License No. 1080

Patent: <http://pat.amgen.com/nplate/>

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 4/2016

Principal Display Panel

Rx Only

NDC 55513-221-01

Amgen®

Nplate®

(romiplostim)

250 mcg*

*Reconstitute with 0.72 mL Sterile Water for Injection, USP.

Delivers 250 mcg in 0.5 mL

For Subcutaneous Use Only

Single Dose Vial; Discard unused portion

Dispense the enclosed Medication Guide to each patient.

Store at 2° to 8°C (36° to 46°F).

Protect from light. Do not freeze.

DO NOT SHAKE reconstituted solution

Rx Only NDC 55513-221-01

AMGEN®

Nplate®
(romiplostim)

250 mcg*

*Reconstitute with 0.72 mL Sterile Water for Injection, USP.

Delivers 250 mcg in 0.5 mL

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Store at 2° to 8°C (36° to 46°F).

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DO NOT SHAKE reconstituted solution

250
mcg*

Rx Only

NDC 55513-222-01

Amgen®

Nplate®

(romiplostim)

500 mcg*

*Reconstitute with 1.2 mL Sterile Water for Injection, USP.

Delivers 500 mcg in 1 mL

For Subcutaneous Use Only

Single Dose Vial; Discard unused portion

Dispense the enclosed Medication Guide to each patient.

Store at 2° to 8°C (36° to 46°F).

Protect from light. Do not freeze.

DO NOT SHAKE reconstituted solution

Rx Only NDC 55513-222-01

AMGEN®

Nplate®
(romiplostim)

500
mcg*

500 mcg*

*Reconstitute with 1.2 mL Sterile Water
for Injection, USP.

Delivers 500 mcg in 1 mL

For Subcutaneous Use Only

Single Dose Vial; Discard unused portion

**Dispense the enclosed Medication
Guide to each patient.**

Store at 2° to 8°C (36° to 46°F).

Protect from light. Do not freeze.

DO NOT SHAKE reconstituted solution

NPLATE

romiplostim injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:55513-222
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ROMPLOSTIM (UNII: GN5XU2DXKV) (ROMPLOSTIM - UNII:GN5XU2DXKV)	ROMPLOSTIM	500 ug in 1 mL

Inactive Ingredients

Ingredient Name	Strength
HYDROCHLORIC ACID (UNII: QTT17582CB)	
HISTIDINE (UNII: 4QD397987E)	10 mmol in 1 mL
MANNITOL (UNII: 3OWL53L36A)	40 mg in 1 mL
POLYSORBATE 20 (UNII: 7T1F30V5YH)	0.04 mg in 1 mL
SUCROSE (UNII: C151H8M554)	20 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-222-01	1 in 1 CARTON	08/25/2008	
1		1 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125268	08/25/2008	

NPLATE

romiplostim injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:55513-221
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ROMPLOSTIM (UNII: GN5XU2DXKV) (ROMPLOSTIM - UNII:GN5XU2DXKV)	ROMPLOSTIM	250 ug in 0.5 mL

Inactive Ingredients

Ingredient Name	Strength
------------------------	-----------------

HYDROCHLORIC ACID (UNII: QTT17582CB)	
HISTIDINE (UNII: 4QD397987E)	5 mmol in 0.5 mL
MANNITOL (UNII: 3OWL53L36A)	20 mg in 0.5 mL
POLYSORBATE 20 (UNII: 7T1F30V5YH)	0.02 mg in 0.5 mL
SUCROSE (UNII: C151H8M554)	10 mg in 0.5 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-221-01	1 in 1 CARTON	08/25/2008	
1		0.5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125268	08/25/2008	

Labeler - Amgen Inc (039976196)

Establishment

Name	Address	ID/FEI	Business Operations
Amgen Manufacturing Ltd		785800020	ANALYSIS(55513-221, 55513-222) , LABEL(55513-221, 55513-222) , PACK(55513-221, 55513-222)

Establishment

Name	Address	ID/FEI	Business Operations
Amgen Technology (ireland) Unlimited Company		896293920	ANALYSIS(55513-221, 55513-222) , LABEL(55513-221, 55513-222) , MANUFACTURE(55513-221, 55513-222) , PACK(55513-221, 55513-222)

Establishment

Name	Address	ID/FEI	Business Operations
Amgen, Inc		039976196	ANALYSIS(55513-221, 55513-222)

Establishment

Name	Address	ID/FEI	Business Operations
Immunex Rhode Island Corporation		968084785	ANALYSIS(55513-221, 55513-222)

Establishment

Name	Address	ID/FEI	Business Operations
Patheon Italia S.p.A.		338336589	ANALYSIS(55513-221, 55513-222) , MANUFACTURE(55513-221, 55513-222)